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Potentially Malignant Disorders – the Case for Intervention

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Abstract

Potentially malignant disorders are recognisable mucosal conditions preceding invasive squamous carcinoma development. Established oral cancer remains a lethal and deforming disease, with a rising incidence. Management techniques for identifiable oral precursor lesions have traditionally been polarised between observational and interventional surgical techniques. By defining salient management goals for treating potentially malignant disease, and examining the evidence supporting the efficacy of treatment intervention, this paper presents the case for interventional laser surgery as a definitive diagnostic and treatment modality.

Introduction

Potentially malignant disorders (PMD) are recognisable oral mucosal lesions, primarily leukoplakia, but also erythroleukoplakia, erythroplakia and proliferative verrucous leukoplakia (PVL), which precede in an unpredictable manner invasive squamous cell carcinoma (SCC) development^{1,2}. Whilst variable malignant transformation rates have been quoted, a systematic review estimated an overall 12% cancer risk over a mean transformation time of 4.3 years³.

The ensuing morbidity and high mortality consequent upon SCC diagnosis and treatment remains significant in contemporary clinical practice and, whilst the objectives of treating PMD have been poorly defined, most authorities agree that prevention of malignancy is the priority⁴. This is complicated, however, by the widespread, often multi-focal nature of disease throughout the upper aerodigestive tract¹.

We have previously defined salient management goals supporting an interventional strategy for PMD management, as outlined in Table 1, and also published a series of long-term patient cohort studies demonstrating the efficacy of intra-oral CO₂ laser surgical excision, both as an accurate diagnostic tool and a reliable treatment modality particularly for managing 'high-risk' PMD⁴⁻⁸. Following initial histopathological diagnosis and risk assessment, mucosal lesions are excised by laser with margins ablated by vapourisation allowing healing by secondary intention⁵. Evidence from a 590 PMD cohort confirmed that interventional surgery provided definitive diagnosis and treatment, facilitated early SCC recognition, identified patients at risk of progressive disease, rationalised follow-up and helped define clinical outcome data⁸.

In a recent journal editorial, however, Guneri & Epstein⁹ repeat a number of previously raised concerns regarding the use of surgical intervention in PMD management. Whilst these are summarised in Table 2, of particular concern are the suggestions of 'over-treatment', 'increased cost of care' and the view that PMD excision 'does not show benefit with respect to progression to cancer'.

For many years, of course, PMD management was controversially polarised between surgical excision to remove identifiable mucosal disease and conservative

medical or observational techniques¹⁰. Shiu & Chen¹¹ attempted a systematic review of treatment efficacy for leukoplakia, but found wide variation in diagnostic criteria, extensive heterogeneity of treatment protocols, disorganised patient compliance and incomplete follow-up data rendering meaningful analyses impossible.

Review of non-surgical managements, including antioxidant and chemotherapeutic approaches, have shown no proven efficacy, demonstrated high risk for side effects, substantive recurrence following treatment cessation and, most pertinently, no evidence of cancer prevention^{10,12,13}. One report observed an increased 31.4% malignant transformation rate in leukoplakia treated with isotretinoin and β -carotene¹⁴, whilst other studies confirmed only 2 to 4% of clinicians would use chemo-preventive agents, emphasising the contemporary redundancy of this modality^{15,16}.

Whilst 'potential malignancy' is undoubtedly a difficult concept for both patients and clinicians, it intuitively warrants interventional management rather than passive observation^{17,18}. van der Waal¹⁹, astutely noting that most PMD patients prefer treatment intervention, recommended surgical excision of localised lesions followed by long-term, specialist follow-up; a view supported by many clinicians^{20,21}.

The aim of this article, therefore, is to review contemporaneous literature regarding PMD treatment and, by addressing each of the stated PMD treatment goals, attempt to clarify the case for interventional surgical management.

Accurate and Definitive Histo-Pathological Diagnosis

Characteristic of PMD is the variable presence of epithelial disorganisation and dysmaturation, identified microscopically as dysplasia and graded subjectively for severity^{1,2}. Although evidence remains weak, it is generally assumed that more severe dysplasia is at greatest risk of cancer development^{1,2}. With no predictive biomarkers available, accurate histo-pathological diagnosis remains essential in clinical practice, yet incision biopsies are not necessarily representative of the true and evolving nature of PMD, particularly large and widespread disorders. A

significant 'under-diagnosis ratio', varying between 14 to 36%, is seen when incision specimens are compared with their excision counterparts²²⁻²⁵.

Incision biopsy, therefore, can only be regarded as a 'provisional' diagnosis, with whole lesion excision deemed mandatory for 'definitive' PMD diagnosis and grading; the latter is facilitated by CO₂ laser excision^{2,4,8,26}. Whilst thermal cytological artefacts at excision margins have been suggested as a limitation of laser biopsy, these do not adversely affect histopathology assessment and reporting by experienced oral pathologists⁵⁻⁸. In addition, it is also recognised that the absence of dysplasia in incision biopsies does not rule out the risk of pre-existing or developing cancer in individual PMD lesions^{25,27}.

Multiple lesion disease, particularly widespread and pan-oral presentation which affects around 25% of PMD patients, is undoubtedly more challenging to manage but the technique of 'field mapping' whereby multiple-site incision biopsies are performed to delineate more significant foci of dysplastic disease facilitates pragmatic, targeted intervention to high-risk regions^{28,29}.

Prediction of Clinical Behaviour

The ability to accurately predict clinical outcome for individual patients or lesions remains elusive in clinical practice^{4,5}. However, long-term follow-up of defined PMD patient cohorts undergoing coordinated interventional treatment has facilitated documentation of clinical outcome and defined categories of disease free, further PMD disease, malignant (same-site) transformation and new-site oral cancer development⁴. Retrospective analyses have identified predictive features: disease free status is more likely in cases of mild dysplasia, but significantly less common with erythroleukoplakia and lesions exhibiting lichenoid inflammation, whilst further disease occurs more frequently in PVL and in the absence of laser excision⁸. The likelihood of SCC development is increased in erythroleukoplakia, in severe dysplasia and in lesions arising on the floor of mouth and ventro-lateral tongue⁸.

As a general observation, the incidence of further disease increases with length of patient follow-up, with non-homogeneous leukoplakia, extensive lesions, more

severe dysplasia and floor of mouth and ventral tongue sites at greatest risk⁷. Continued tobacco smoking and alcohol remain persistent risk factors following laser surgery risking development of further PMD^{7,30}.

Early Recognition of Malignancy

Sufficient evidence exists to confirm that PMD excision facilitates early recognition of cancer. Review of surgically treated cases shows that ‘unexpected’ SCCs, often at early invasive stages, are identified histo-pathologically in 7 to 12% of excision specimens^{8,23-25,31}; a figure not dissimilar to the 12% transformation rate quoted in systematic review³ and an important diagnostic and treatment success. The efficacy of intervention is confirmed in our study cohorts because few patients required post-laser oncology treatment and long-term follow-up revealed excellent clinical outcomes^{7,8,25}.

SCC detection at an early stage enables curative treatment with simple and minor surgical intervention^{4,32}. In contrast, the limitations of PMD observation are highlighted by a 25% malignant transformation rate reported in a UK dysplasia clinic where there was no coordinated treatment protocol and SCC diagnoses only made following clinically evident malignant change³².

Effective Removal of Premalignant Tissue

As mucosal-only conditions, PMDs do not require the extensive treatment necessary for SCC removal or destruction. It seems self-evident to intervene early and remove dysplastic mucosa whilst ‘pre-invasive’. Surgery can be performed by scalpel, cutting diathermy or photodynamic therapy but the efficacy of dysplasia excision by CO₂ laser is confirmed in patient cohort studies⁵⁻⁸. Dysplasia-free margins or residual foci of mild dysplasia are seen in 75% of treated cases^{7,30}, but with no significant association between dysplasia in resection margins and clinical outcome, almost certainly due to the ability to extend treatment zones by laser ablating oral cavity margins 2-4mm beyond specimen excision⁴.

Whilst minimal intervention has been proposed for less severely dysplastic lesions, treatment of all mucosal pre-malignancy is recommended to reduce risks of recurrence and disease progression consequent upon observing even mildly dysplastic lesions^{33,34}.

Prevention of Further Disease

Well-defined clinical outcome categories are essential prerequisites to inform clinical practice and improve understanding of PMD natural history^{1,2}. Review of CO₂ laser treatment studies shows that 51 to 89% of PMD patients are rendered free of disease, with only 10 to 34% exhibiting further disease^{8,35-40}; this contrasts with observational treatment in which 77% of lesions persist⁴¹.

Following successful primary therapy, local PMD recurrence and development of new-site lesions may occur⁴², but careful patient follow-up facilitates early identification and further laser treatment can be administered. Whilst most patients in our study series required only 1 laser treatment, a mean number of 2.26 treatments over a mean time of 32.9 months ultimately rendered over 74% of 590 PMD patients disease free despite initial presentation with significant dysplasia⁸.

Prevention of Malignant Transformation

It is a fundamental hypothesis, and the most significant justification for PMD intervention, that surgical removal of a dysplastic lesion will reduce the risk of malignant transformation. Studies have shown 15% transformation rates for patients whose lesions were not excised, compared with around 5-6% where lesions were removed^{3,43}.

Excluding SCCs excised 'unexpectedly', we have noted between 2 to 5% of PMD patients developing same or new-site cancer formation during post-treatment follow-up⁵⁻⁸. Local surgical excision of dysplastic lesions appears to decrease the risk of same-site malignant transformation, but does not eliminate the risk of new-site oral cancer development^{13,34,44}. The clinical consequence is the realization that continued

patient surveillance, regular clinic monitoring and risk factor profiling remain pertinent for all PMD cases following treatment⁴.

Patient Acceptability and Minimal Morbidity

As CO₂ laser surgery is recommended as the preferred PMD management choice, it is important that it is both acceptable to patients and post-operative morbidity is low. Significant complications following CO₂ laser treatment are rare and, whilst some patients report post-operative pain, submandibular salivary gland swelling following floor of mouth procedures and lingual nerve dysaesthesia after tongue surgery, these are usually transient, self-limiting and rarely require additional treatment^{6,45}. A small number of patients report prolonged complications but these are usually after more extensive surgery, or in those who continue to smoke heavily or consume alcohol after treatment⁴⁵.

In general, laser surgery is well tolerated and accepted by patients, aids haemostasis, promotes excellent healing and produces minimal scarring with little functional deficit or patient morbidity⁵. A particular advantage is the ability to repeat excisions or ablations at the same site without compromising oral healing or function^{4,5}. No significant adverse quality of life outcomes for PMD patients have been reported, particularly in contrast to the known physical and psycho-social consequences of SCC treatment⁴⁶.

Whilst no consensus exists to determine the nature or duration of PMD follow-up, a policy of active surveillance offers patients a number of additional treatment advantages and helps advance understanding of PMD natural history and disease progression⁵; Table 3. Interventional management should be considered cyclical in nature, passing from active surgical excision through to surveillance but returning to surgical intervention upon diagnosis of further disease. It is, therefore, a consistent and determined approach to patient management^{4,5}.

Cost Effectiveness

Few data exist in the literature to support or refute the concept that early, minimal intervention, essentially secondary or tertiary SCC prevention in 'at risk' populations, is cost-effective, but it is not an unreasonable hypothesis. Rather than increasing cost of care, targeted PMD excision is likely to prove less expensive than the alternative of multiple, repeat incision biopsies performed over many years of observational follow-up⁴⁴. There may be additional cost savings in centralizing services for PMD patients within specialist oral oncology centres⁵.

In considering wider aspects of health economics, it is necessary to balance PMD treatment efficacy, cost and value for money with anticipated costs of oncology treatment. Recently introduced UK Department of Health Patient-Level Information and Costing Systems (PLICS) allow estimates of costs incurred by NHS healthcare organizations providing specific treatments. PLICS data from the Newcastle upon Tyne Hospitals NHS Foundation Trust over 6 months (April-October 2015) contrasted diagnostic and surgical services for PMD laser surgery (averaged at around £997.90 per treated patient) with multi-disciplinary SCC care (£5,471.58 per patient). Initial SCC treatment cost more than 5 times PMD management, without considering the significant additional costs of head and neck cancer care, including adjuvant radiotherapy and/or chemotherapy treatments.

Conclusions

Clinical outcomes for oral cancer will only improve by earlier detection of SCC and effective management of precursor lesions with malignant potential⁴⁷. The consequences for an individual patient progressing to SCC are devastating. There seems little to gain from observational strategies, particularly as substantive evidence, summarised in Table 4, supports the diagnostic and treatment efficacy of intervention as a definitive treatment modality. Interventional laser surgery provides readily available, effective, low morbidity treatment which is successful in excising PMD mucosal lesions, facilitates early diagnosis of occult SCC and may help reduce overall risk of SCC development.

In the future, PMD patients will require better stratification into 'high' and 'low' risk categories, with individually tailored treatment protocols based upon bio-molecular and genetic profiling of cancer risk. Whilst awaiting such refinements, and in the absence of meaningful multi-centre, prospective randomised trials, the contemporary case for interventional management is presented.

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Competing Interests

None declared.

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TABLE 1: MANAGEMENT GOALS IN TREATING PMD

Management Goals
Accurate Diagnosis
Prediction of Clinical Behaviour
Early Recognition of Malignancy
Removal of Dysplastic Mucosa
Prevention of Further Disease
Prevent Malignant Transformation
Patient Acceptability and Minimal Morbidity
Cost-Effective

TABLE 2: PERCEIVED CRITICISM OF INTERVENTIONAL PMD TREATMENT

Risk of 'over-treatment' of benign lesions unlikely to progress to cancer
Cost of treatment
Intervention does not reduce the risk of cancer
Uncertainty over placement and significance of excision margins
Risk of PMD recurrence
No ability to predict clinical behaviour
Poor functional outcome following treatment of widespread lesions

TABLE 3: ADVANTAGES OF PATIENT FOLLOW-UP AND SURVEILLANCE STRATEGIES

POST- PMD TREATMENT

Assess efficacy of treatment intervention
Recognise treatment complications
Early identification of recurrent or further PMD disease
Early identification of cancer development
Optimal timing and coordination of further treatment intervention
Opportunities to modify patient risk factor behaviour
Effective assessment of long-term patient risk
Improve understanding of PMD natural history

TABLE 4: PMD MANAGEMENT GOALS AND TREATMENT EFFICACY

		Treatment	Modality	
Management Goals	Observation	Medical Therapy	Laser Surgery	References
Accurate Diagnosis	No	No	Yes	22, 23, 24, 25, 26, 27, 28, 29
Prediction of Clinical Behaviour	No	No	Possible	4, 7, 8, 30
Early Recognition of Malignancy	No	No	Yes	8, 23, 24, 25, 31, 32
Removal of Dysplastic Mucosa	No	No	Yes	4, 5, 6, 7, 8, 30, 33, 34
Prevention of Further Disease	No	No	Possible	8, 35, 36, 37, 38, 39, 40, 41, 42
Prevent Malignant Transformation	No	No	Possible	3, 4, 5, 6, 7, 8, 13, 34, 43, 44
Patient Acceptability and Minimal Morbidity	No	No	Yes	4, 5, 6, 45, 46
Cost-Effective	?	?	Yes	5, 44